Patents

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re Application of: | **Richard I. Weiner, et al.** | Conf. #: **5766** |
| Serial No. | **10/714,067** | Art Unit: **1647** |
| Filed: | **November 14, 2003** | Examiner: **Christine J. Saoud** |
| For: | **NOVEL ANTIANGIOGENIC PEPTIDE AGENTS AND THEIR THERAPEUTIC AND DIAGNOSTIC USE** | |

**DECLARATION UNDER 37 C.F.R. § 1.132**

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Joseph A. Martial, Ph.D., hereby declare that:

1. I am a Professor employed by the University of Liège, the licensee of the above-identified patent application.

2. I am an inventor for the above-referenced patent application.

3. I have over 30 years of experience working in the field of molecular biology and genetic engineering.

4. I have reviewed the above-referenced patent application, the current amendments, and the Office Action mailed July 11, 2006, in connection with the above-referenced patent application.

5. The Office Action is incorrect in its characterization of the Heymsfield et al. reference and the Reagan et al. reference.

6. Following digestion of growth hormone with plasmin, the resulting 133 amino acid N-terminal fragment of growth hormone is strongly associated with the C-terminal fragment of growth hormone.

7. Because of this strong association of the fragments, it is not possible to successfully separate the N-terminal fragment from the C-terminal fragment of growth hormone by using standard non denaturating procedures such as Sephadex gel filtration or ion exchange chromatography.

8. To study the effect of the N-terminal fragment of growth hormone in isolation, we developed a method as described in the present application in which the 133 amino acid N-terminal fragment of growth hormone may be produced in the absence of the remaining fragment of growth hormone. In particular, a nucleic acid encoding the N-terminal fragment of growth hormone was cloned into an expression vector, and the fragment was expressed in *E. coli* and purified to a level of purity in which the N-terminal fragment was greater than 80% of the molecules in the composition. We verified that this N-terminal fragment was totally devoid of the activity of the intact growth hormone.

9. Heymsfield et al. teach the plasmin hydrolysis of growth hormone. However, they do not teach any separation of the fragments created by the plasmin hydrolysis. They do not teach a composition in which the N-terminal fragment is greater than 80% of the molecules in the composition.

10. Reagan et al. teach the separation of the major components of the plasmin digest of reduced and S-carbamidomethylated human growth hormone (RCAM-hGH) from small

cleavage products into five groups by gel filtration on Sephadex G-50 in 0.01 N HCl (page 1686, Figure 2).

11. Reagan et al. indicate that the Peak 1 from that column appeared to have a mixture of undigested precursor and aggregated digestion products, and Peak 5 was determined to contain a hexapeptide (residues 135-140)(page 1686).

12. Reagan et al. showed that Peak 2 had the biological properties of an intact growth hormone (page 1686, first full paragraph).

13. "Peaks 3 and 4" are not actually peaks, but rather are a mixture of different molecules and cannot contain one particular molecule at a level of purity in which that particular molecule is 80% or greater of the molecules present in the population.

14. Reagan et al. took no further action to separate the N-terminal fragment of growth hormone from the C-terminal fragment, and therefore, Peak 2 contains the N-terminal fragment associated with the C-terminal fragment and not an isolated N-terminal fragment.

15. The fact that Peak 2 in Reagan et al. contains the associated fragments is supported by the findings of Cunningham et al., 1989, Science 243:1330-36. Cunningham et al. identified two binding domains on human growth hormone that are involved in binding of human growth hormone to its receptor. One binding domain required for binding is present on the N-terminal fragment, however, a second binding domain is present on the smaller C-terminal fragment. Accordingly, because Peak 2 in Reagan et al. retained the activity of the intact growth hormone (*i.e.* stimulating weight gain, cartilage metabolism, and glucose oxidation), both binding domains must have been present on the molecule in that fraction eluted from the column.

The N-terminal fragment has only one of the binding domains, and therefore, does not retain the biological activities of the intact growth hormone.

16. The discussion presented herein demonstrates that the cited references do not teach an isolated N-terminal fragment of growth hormone because neither of the cited references achieve the required purity of the fragment.

17. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Joseph A. Martial — Nov. 10, 2006

**Joseph Martial, Ph.D.** — **Date**